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High Prevalence but Low Impact of Cognitive Dysfunction on Quality of Life in Patients With Lupus and Neuropsychiatric Symptoms

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Objective. To evaluate the prevalence and impact of cognitive impairment on health-related-quality of life (HRQoL) in patients with systemic lupus erythematosus (SLE) and neuropsychiatric (NP) symptoms.

Methods. Patients with SLE and NP symptoms referred to the Leiden NPSLE clinic (2007–2019) were included. In a multidisciplinary evaluation, NP symptoms were attributed to SLE (NPSLE: inflammatory, ischemic, or both combined) or other causes. Four cognitive domains were determined: global cognitive function (score 0–30), learning and memory, executive function and complex attention, and psychomotor speed (all T scores). HRQoL was determined using the mental component score and physical component score of the Short Form 36 health survey. The associations between cognition and NPSLE phenotype and cognition and HRQoL were assessed with multiple regression analyses and linear mixed models corrected for confounding and expressed in SDs.

Results. A total of 357 patients (86% female, mean age 44 years) were included. Of those 357 patients, 169 had a follow-up visit (median follow-up 11 months). Impairment in global cognitive function was present in 8% of patients, and in all other cognitive domains in ±50%. The most severe impairment (all domains) was seen in patients with a combined NPSLE phenotype. Diffuse cognitive impairment (learning and memory, executive function and complex attention, and psychomotor speed) was most common and was present more often in patients with an inflammatory phenotype. A weak association between cognition and HRQoL was found both cross-sectionally and longitudinally. In general, 1 SD lower scores on the cognitive domains were associated with at most one-fifth SD lower HRQoL.

Conclusion. Objective cognitive impairment is common in SLE patients with NP symptoms, but may have a limited influence on HRQoL.

INTRODUCTION

Cognitive dysfunction is a common diffuse central nervous system manifestation of systemic lupus erythematosus (SLE). Due to the lack of uniform screening tools and heterogenous study populations, the reported prevalence of cognitive dysfunction in patients with SLE varies greatly, most estimates ranging from 15% to 80% (1–4). Cognitive dysfunction is defined by the American College of Rheumatology (ACR) nomenclature as "significant deficits in any or all of the following main cognitive functions: memory (learning and recall), complex attention, simple attention, executive skills (planning, organizing, and sequencing), visual-spatial processing, language (e.g., verbal, fluency), reasoning/problem solving, and psychomotor speed." Specific domains, such as attention and memory, are known to be particularly affected in patients with SLE (4).

Different mechanisms may be involved in the development of cognitive dysfunction in patients with SLE. SLE activity itself may lead to central nervous system inflammation, which may result in cognitive dysfunction (5,6). In addition, cognitive dysfunction may be the consequence of vascular injury, for example due to the presence of antiphospholipid antibodies (7). Other factors,

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SIGNIFICANCE & INNOVATIONS

- Cognitive function may be affected in patients with systemic lupus erythematosus, and impairment is frequently experienced as burdensome.
- In patients with lupus presenting with neuropsychiatric symptoms, objective cognitive function is frequently impaired, but only weakly associates with quality of life.
- To improve quality of life in patients with lupus, we suggest that research should focus on which underlying processes determine the lower quality of life, such as depression and anxiety, rather than objective cognitive impairment.

such as anxiety, depression, stress, fatigue, and medication have also been implied as important causes (8,9). Whether the underlying etiology influences the type and severity of cognitive dysfunction is insufficiently known. In general, cognitive dysfunction attributed to SLE activity (neuropsychiatric lupus [NPSLE]) is associated with more severe impairment (10,11).

Factors associated with cognitive dysfunction, such as anxiety and depression, are known to negatively affect quality of life (QoL) (12,13). However, to date only a limited number of studies have investigated the direct influence of cognition on QoL in patients with SLE (14–16). Different measurements of cognition (subjective and objective) have been used and mostly in models to predict QoL, rather than to look at causal associations. Therefore, the impact of cognition on QoL in patients with SLE remains unascertained.

The aim of this study was 2-fold. First, we wanted to identify the type and severity of objective cognitive dysfunction in patients with SLE and NP symptoms of different origins. Second, the goal was to study the association between objective cognitive functioning and QoL.

PATIENTS AND METHODS

Study design and population. All patients visiting the Leiden University Medical Center (LUMC) NPSLE tertiary referral center between 2007 and 2019 with written informed consent and the clinical diagnosis of SLE were included in this study. The NPSLE clinic has been described in detail previously (17). In summary, patients with a diagnosis (or suspected diagnosis) of SLE who present with NP symptoms are referred to the LUMC NPSLE clinic and are evaluated by a multidisciplinary team, including a rheumatologist, neurologist, clinical neuropsychologist, psychiatrist, neuroradiologist, and vascular internist. A broad definition of NP symptoms is used, defined as neurologic, psychiatric, or true NP symptoms (as in existing literature) (18). A consensus meeting takes place, in which symptoms are attributed to SLE (major NPSLE) or to other causes and/or NP symptoms for which symptomatic treatment suffices (minor/non-NPSLE). In the case of major NPSLE, NPSLE phenotypes are determined based on clinical, serologic, and radiologic assessment: inflammatory, ischemic, or a combination thereof (19). Therefore, 4 phenotypes are present in this study: minor/non-NPSLE and 3 subtypes of major NPSLE: inflammatory NPSLE, ischemic NPSLE, and combined NPSLE. NPSLE syndromes are assigned according to the 1999 ACR case definitions for NPSLE (18). A total of 371 patients were eligible for this study, of which 357 patients had a neuropsychological assessment and were included in this study (see Supplementary Appendix A [Supplementary Table 1], available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24904). Permission for this study was obtained from the Leiden-The Hague-Delft medical ethical committee (P07.177).

Patient characteristics. Patient information was collected during patient interviews and later retrieved from electronic medical files. The following patient characteristics were collected: age, sex, smoking status, the presence of diabetes mellitus and antiphospholipid syndrome (20), SLE duration, Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) score (21), Systemic Lupus International Collaborating Clinics (SLICC)/ACR Damage Index score (22), 1997 ACR classification criteria for SLE (23), education level (low: 0–6 years, middle: 7–12 years, high: >12 years), the presence or absence of major NPSLE, NPSLE phenotype, or NPSLE syndrome (18), and the presence of a depressive or an anxiety disorder according to the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) (24).

Cognitive assessment. All patients received an extensive neuropsychological assessment on the day of the visit to the NPSLE clinic, adapted from the neuropsychological test battery as suggested by the 1999 ACR NPSLE nomenclature and case definition system (18). For this study, the following neuropsychological tests were included: Minimal Mental State Examination (MMSE) (25), Wechsler memory scale (26), STROOP color and word test (27), and trail-making test (TMT) (28). As described in detail previously (29), these tests are categorized in 4 cognitive domains, as suggested by the DSM-V (24): 1) global cognitive function: MMSE (total score); 2) learning and memory: Wechsler Memory Scale (T score); 3) executive function and complex attention: STROOP3 (T score) and TMT-B (T score); and 4) psychomotor speed: STROOP1 + 2 (time) and TMT-A (T score).

For the global cognitive function domain, moderate cognitive impairment was defined as a score of ≤25 of 30 and severe impairment as a score of ≤20 of 30. For the 3 other cognitive domains, moderate impairment was defined as a score of ≥1 SD lower than the Dutch general population (i.e., T score ≤40) (30), and severe impairment as a score of ≥2 SD lower than the Dutch general population (i.e., T score ≤30). In cognitive domains

consisting of multiple tests (executive function and complex attention and psychomotor speed), scores were averaged. If individual test scores were missing, the T score of that domain was based only on the available tests.

Health-related QoL. All patients received the Dutch version of the Short Form 36 health survey (SF-36) at the visit to the NPSLE clinic. The SF-36 is a self-administered validated questionnaire to assess health-related QoL (HRQoL) (31). The SF-36 consists of 8 domains of health status: physical functioning, physical role limitations, bodily pain, general health perceptions, energy/vitality, social functioning, emotional role limitations, and mental health. Individual test scores are transformed to range from 0 (worst possible health) to 100 (best possible health) (32). A scoring algorithm is used to convert these transformed scores into the 8 domains listed above. For this study, the summary mental component score (MCS) and physical component score (PCS) were calculated using norm-based scoring, which employs linear transformation to achieve standardized scores with a mean ± SD of 50 ± 10 for each dimension by using the Dutch general population as a reference group (31). Higher PCS and MCS indicate a better HRQoL.

Follow-up assessment. Follow-up visits take place on indication, such as initiation of immunosuppressive treatment in patients with inflammatory/combined NPSLE or uncertainty about attribution of NP symptoms to SLE (2007–2019). A number of patients (~25%) received follow-up for research purposes between 2013 and 2014. All follow-up visits are identical to the baseline visits and include among other items questionnaires and neuropsychological assessment.

Statistical analysis. Distributions of continuous variables were visually inspected using histograms. Baseline characteristics were presented as mean ± SD for normally distributed continuous variables, as median with interquartile range (IQR) for non-normally distributed continuous variables, and as percentages for categorical variables.

Cognition was compared at baseline between different NPSLE phenotypes (minor/non-NPSLE, inflammatory, ischemic, and combined) using multivariable regression analyses, corrected for age, sex, education level, and psychiatric morbidity. An additional analysis was performed comparing frequency and type of cognitive impairment in patients with and without a depressive disorder. Cognition was compared in individuals with a baseline and follow-up within 2 years using Wilcoxon's signed-rank test (global cognitive function, non-normal distribution) and paired *t*-tests (all other cognitive domains, normal distribution) in all patients and per NPSLE phenotype. The median difference (95% confidence interval [95% CI]) for global cognitive function and mean differences (95% CI) for all other cognitive domains were calculated.

The main analyses to assess associations between cognition and HRQoL (MCS/PCS) were multivariable regression analyses per cognitive domain, corrected for the potential confounding variables of age, sex, education, smoking, diabetes mellitus, and psychiatric morbidity. Cognition and HRQoL were both evaluated at baseline (cross-sectionally). As additional analyses, associations between cognitive function and HRQoL (MCS/PCS) were assessed after a median of 11 months of follow-up (longitudinally) in all patients with a follow-up visit using a linear mixed model. Time and confounding variables (age, sex, education, smoking, diabetes mellitus, and psychiatric morbidity) were modeled using fixed effects. All models included random intercept and slope to account for the longitudinal aspect of the data, and an unstructured correlation matrix was used.

Missing data. Cognitive assessment was unavailable for 14 patients (4%). Reasons for lack of cognitive assessment were missing documentation (n = 6), severe disease (e.g., coma or catatonic state, n = 4), language barrier (n = 2), recent full cognitive assessment elsewhere (n = 1), and severe visual disturbance (n = 1). In addition, elements of the cognitive assessment were missing in some of the remaining patients (n = 357): global cognitive function (n = 5, 1%), learning and memory (n = 3, 1%), executive function and complex attention (n = 26, 7%), and psychomotor speed (n = 14, 4%). QoL assessment (SF-36) was missing in 25 patients (7%). Complete case analyses were performed as main analyses and several imputation methods were used as sensitivity analyses.

Sensitivity analyses. Multiple sensitivity analyses were performed. To ascertain the quality of our data as well as the validity of our methodology, known clinical phenotypes, namely the associations between depression and HRQoL (MCS) and anxiety and HRQoL (MCS) were assessed using multivariable regression analyses corrected for age, sex, and education. Furthermore, 2 analyses were performed to assess the influence of missing data. First, the association between cognition and HRQoL was studied after multiple imputation using chained equation of missing HRQoL data. Second, analyses were repeated after imputation of missing cognitive data with the value of the 25th, 10th, and 5th percentile from the available data of the missing cognitive domain. In addition, an alternative statistical method to assess the association between cognition and HRQoL was performed: linear regression analyses for the longitudinal analysis instead of linear mixed models. All sensitivity analyses are reported in Supplementary Appendix B, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24904. All statistical analyses were performed using Stata statistical software, version 16. Figures were created using R software, version 4.1.2. (package: UpSet) and Graphpad Prism software, version 9.0.1.

Table 1. Baseline characteristics of 357 patients referred to the LUMC NPSLE clinic*

Characteristic	NPSLE clinic 2007–2019 (n = 357)
Demographic characteristics	
Female	308 (86)
Age, mean ± SD years	44 ± 14
Education	
Low	15 (4)
Middle	230 (64)
High	112 (32)
Current smoking	101 (28)
SLE characteristics, median (IQR)	
Duration of SLE, years	4 (1–13)
SLEDAI-2K	4 (2–8)
SDI	1 (0–2)
Comorbidities	
Diabetes mellitus	15 (4)
Antiphospholipid syndrome	67 (19)
Depressive disorder	80 (22)
Anxiety disorder	17 (5)
Attribution of NP symptoms	
Major NPSLE	
Inflammatory	49 (14)
Ischemic	29 (8)
Combined	25 (7)
Minor/non-NPSLE	254 (71)

* Values are the number (%), unless indicated otherwise. IQR = interquartile range; LUMC = Leiden University Medical Center; NP = neuropsychiatric; SDI = Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; SLE = systemic lupus erythematosus; SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index 2000.

RESULTS

Study population. A total of 357 patients were included in this study (see Supplementary Figure 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24904). The majority of patients were female (86%) and mean ± SD age was 44 ± 14 years. The median SLE disease duration was 4 years (IQR 1–13), and the median disease activity as measured by SLEDAI-2K was 4 (IQR 2–8) (Table 1). Most patients (64%) received education for 7–12 years. A depressive disorder according to the DSM-V was present in 80 patients (22%) at study visit. After multidisciplinary assessment, NP symptoms were attributed to SLE (major NPSLE) in 103 patients (29%) and an inflammatory phenotype was the most common subtype of NPSLE (49 of 103). The type of NPSLE syndromes present according to the 1999 ACR case definitions is provided in Supplementary Table 1, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.24904. In total, 169 patients (47%) had a follow-up visit, with a median follow-up time of 11 months (IQR 6–28).

Cognitive impairment. In the entire study population (n = 357), cognitive impairment was common (Figure 1 and Supplementary Table 2, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24904). The global cognitive function domain was the least affected, with moderate impairment present in 6% and severe impairment in 2% of the 352 patients in whom global cognitive function was

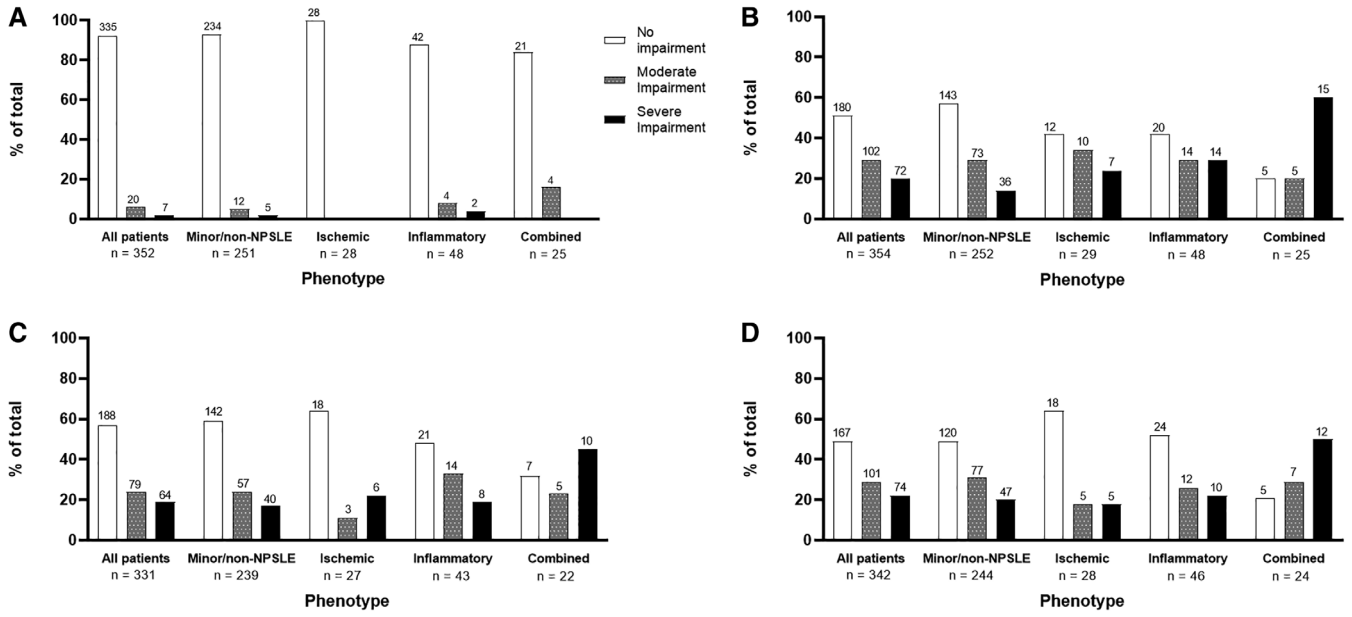

Figure 1. Prevalence of impairment in different cognitive domains in patients with systemic lupus erythematosus (SLE) and neuropsychiatric symptoms of different origins visiting the Leiden University Medical Center clinic between 2007 and 2019. The y axis represents the percentage of patients within different categories, whereas the numbers above the bars show the number of patients. **A**, Global cognitive function (n = 352), **B**, Learning and memory (n = 354), **C**, Executive function and complex attention (n = 331), **D**, Psychomotor speed (n = 342). NPSLE = neuropsychiatric SLE.

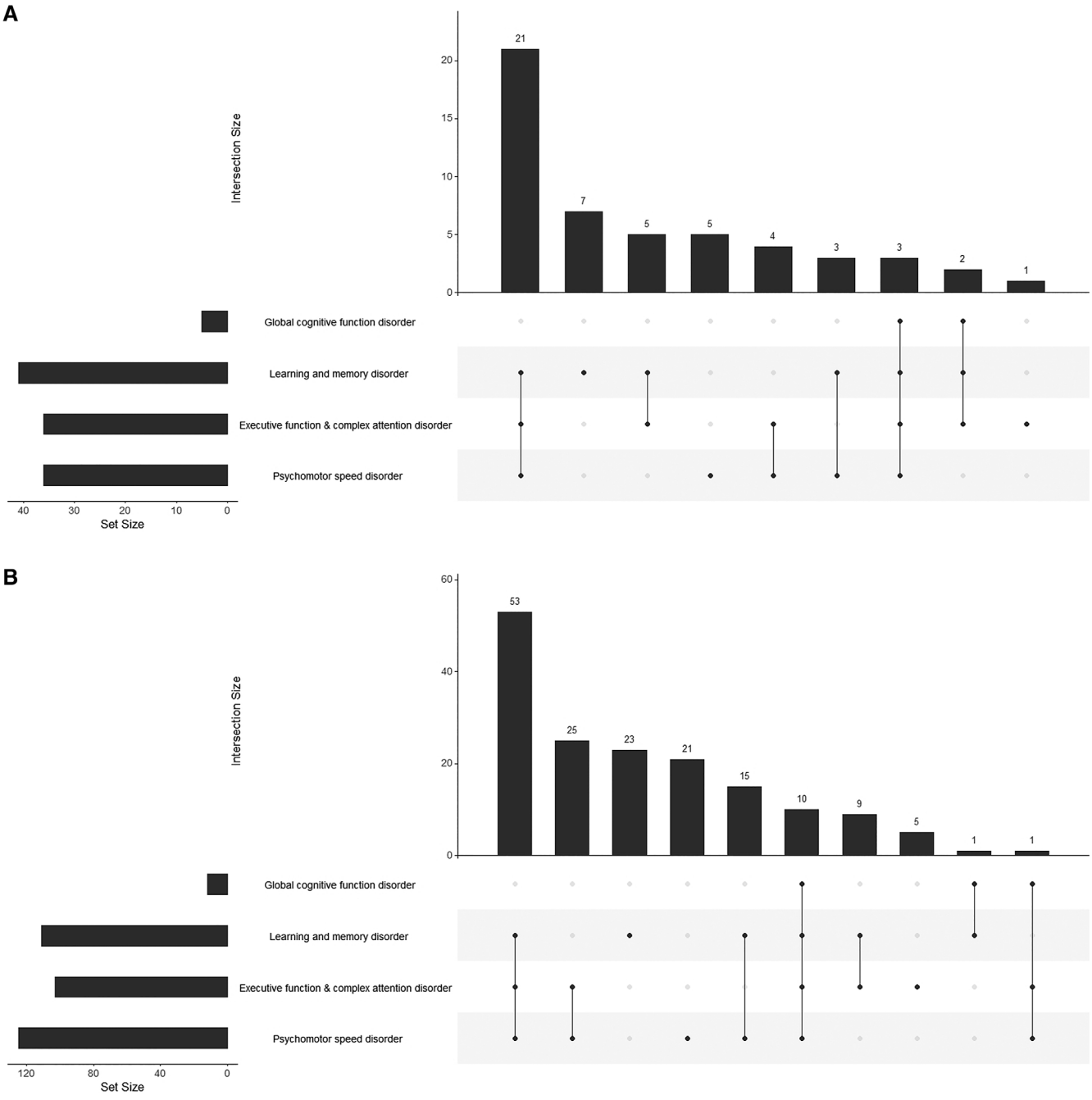

Figure 2. Pattern of cognitive impairment in patients with systemic lupus erythematosus (SLE) and neuropsychiatric symptoms with **A**, Inflammatory phenotype (inflammatory or combined neuropsychiatric SLE, n = 64), or **B**, Noninflammatory phenotype (ischemic neuropsychiatric SLE or other causes, n = 260). Connected dots show which domains are impaired simultaneously. Only patients who had complete assessment of all 4 cognitive domains (n = 324) were included in this figure.

assessed. All other cognitive domains were impaired in approximately one-half of the patients: moderate and severe impairment occurred in the domain learning and memory in 29% and 20%, respectively, of the 354 patients; in the domain executive function and complex attention, moderate and severe impairment were 24% and 19%, respectively, of the 331 patients, and in the domain psychomotor speed, moderate and severe impairment were 29% and 22%, respectively, of the 342 patients. This high level of cognitive impairment was seen in all NPSLE phenotypes and was most pronounced in major NPSLE with a combined phenotype (Figure 1). This finding was confirmed using multivariable regression analyses; after correction for age, sex, education, and psychiatric morbidity, patients without major NPSLE generally performed better than patients with major NPSLE. This difference was only statistically significant in patients with a combined NPSLE phenotype (see Supplementary Table 3, available on the *Arthritis Care &*

Table 2. Cognitive function at baseline and follow-up visit within 2 years in patients with SLE and neuropsychiatric symptoms (total n = 357)*

Cognitive domain	Total study population, baseline	All patients with follow-up ≤2 years (n = 122)		
		Baseline	Follow-up	Difference (95% CI)†
Global cognitive function	28 (27–30)	28 (27–29)	29 (27–30)	0.7 (0.6, 0.7)
T score, mean ± SD				
Learning and memory	37.8 ± 13.8	35.1 ± 16.8	38.8 ± 17.1	3.7 (1.9, 5.5)
Executive function and complex attention	40.5 ± 13.2	38.4 ± 14.4	42.8 ± 13.0	4.4 (2.6, 6.3)
Psychomotor speed	38.5 ± 12.2	36.2 ± 12.7	38.9 ± 12.4	2.6 (0.9, 4.5)

* Values are the median (interquartile range) unless indicated otherwise. 95% CI = 95% confidence interval; SLE = systemic lupus erythematosus.
† Median difference (95% CI) for global cognitive function and mean difference (95% CI) for all other domains.

Research website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24904). Patients with a combined phenotype had a T score of ~10 points lower (1 SD of the normal Dutch population) than patients with minor/non-NPSLE on 3 of 4 cognitive domains. Furthermore, the pattern of cognitive impairment was evaluated in patients who had information on all 4 cognitive domains (n = 324). The most common pattern was a combination of impairment in learning and memory, executive function and complex attention, and psychomotor speed. This pattern was observed more frequently in patients with an inflammatory origin of NP symptoms (inflammatory/combined phenotype) than NP symptoms of other origin (21 of 64 [33%] versus 53 of 260 [20%]) (Figure 2).

As depression was frequently present (22%) and is known to influence cognitive performance, a comparison of cognitive impairment was made between patients with (n = 80) and without (n = 277) a depressive disorder. Severe cognitive impairment was more frequent in patients with depression than without in the domains executive function and complex attention and psychomotor speed. The other domains were similar (see Supplementary Table 4, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24904).

Cognition was also evaluated over time in 122 patients with a follow-up visit within 2 years. In all cognitive domains, an improvement was seen over time (Table 2). The median change of global cognitive function score was 1 (95% CI 0.5, 1.5). The mean change was 3.7 (95% CI 1.9, 5.5) for learning and memory, 4.4 (95% CI 2.6, 6.3) for executive function and complex attention, and 2.6 (95% CI 0.9, 4.5) for psychomotor speed. Additional analyses revealed that patients with an inflammatory and combined phenotype showed the most improvement at follow-up in all cognitive domains (see Supplementary Table 5, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24904).

Cognition and HRQoL. HRQoL assessment was available for 332 patients. Mean ± SD MCS was 37.8 ± 12.8 and PCS was 36.6 ± 10.0. The association between cognition and HRQoL was assessed cross-sectionally (Table 3). An association was found between cognition and MCS in nearly all cognitive domains. For global cognitive function, the association after adjustment was B = 0.56 (95% CI 0.07, 1.22; score 0–30); for learning and memory B = 0.19 (95% CI 0.07, 0.31); for executive function and complex attention B = 0.12 (95% CI 0.02, 0.22), and for psychomotor speed B = 0.07 (95% CI –0.04, 0.18) (T scores). This result means that, for example, a 10-point higher T score (= 1 SD of the general Dutch population) on the learning and memory domain was associated with a 1.9 point higher (approximately one-fifth SD of the general Dutch population) MCS in our study. An association was also found between cognition and PCS in nearly all cognitive domains: for global cognitive function B = 0.37 (95% CI –0.14, 0.87), for learning and memory B = 0.14 (95% CI 0.04, 0.25); for executive function and complex attention B = 0.16 (95% CI 0.07, 0.25), and for psychomotor speed B = 0.21 (95% CI 0.12, 0.31). Additional analyses assessing the association between cognition and the 8 domains of HRQoL separately were unremarkable (see Supplementary Table 6, available

Table 3. Association between baseline cognition and baseline quality of life in patients with SLE and neuropsychiatric symptoms (n = 332)*

Cognitive domain	B	Adj B (95% CI)†
Mental component score		
Global cognitive function‡	0.56	0.64 (0.07, 1.22)
Learning and memory (T score)	0.20	0.19 (0.07, 0.31)
Executive function and complex attention (T score)	0.16	0.12 (0.02, 0.22)
Psychomotor speed (T score)	0.12	0.07 (–0.04, 0.18)
Physical component score		
Global cognitive function‡	0.49	0.37 (–0.14, 0.87)
Learning and memory (T score)	0.15	0.14 (0.04, 0.25)
Executive function and complex attention (T score)	0.16	0.16 (0.07, 0.25)
Psychomotor speed (T score)	0.21	0.21 (0.12, 0.31)

* For all T scores and the mental component score plus physical component score, 10 points = 1 SD of the Dutch general population. Example interpretation: 10 points higher learning and memory score (= 1 SD) is associated with a 1.9-point higher score on the mental component score (= one-fifth SD). 95% CI = 95% confidence interval; SLE = systemic lupus erythematosus.
† These data represent B values and 95% CIs resulting from multiple regression analyses corrected for age, sex, education, psychiatric morbidity, diabetes mellitus, and smoking.
‡ Global cognitive function: Minimal Mental State Examination score (raw score range 0–30).

Table 4. Association between cognition and quality of life over time in patients with SLE and neuropsychiatric symptoms (n = 169)*

Cognitive domain	B	Adj B (95% CI)†
Mental component score		
Global cognitive function‡	0.56	0.68 (0.19, 1.16)
Learning and memory (T score)	0.18	0.18 (0.09, 0.27)
Executive function and complex attention (T score)	0.18	0.14 (0.05, 0.23)
Psychomotor speed (T score)	0.14	0.10 (0.01, 0.19)
Physical component score		
Global cognitive function‡	0.59	0.44 (0.03, 0.85)
Learning and memory (T score)	0.16	0.15 (0.08, 0.22)
Executive function and complex attention (T score)	0.14	0.13 (0.06, 0.21)
Psychomotor speed (T score)	0.17	0.17 (0.09, 0.24)

* For all T scores and the mental component score plus physical component score, 10 points = 1 SD of the Dutch general population. Example interpretation: 10 points higher learning and memory score (= 1 SD) is associated with a 1.9-point higher score over time on the mental component score (= one-fifth SD). 95% CI = 95% confidence interval; SLE = systemic lupus erythematosus.
† These data represent B values and 95% CIs resulting from linear mixed models corrected for age, sex, education, psychiatric morbidity, diabetes mellitus, and smoking.
‡ Global cognitive function: Minimal Mental State Examination score (raw score range 0–30).

on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24904). The longitudinal analyses with the patients who had a follow-up visit (n = 169) showed nearly identical results to the cross-sectional analyses (Table 4).

Sensitivity analysis findings. As quality assurance, the association between depression and HRQoL and anxiety and HRQoL was assessed. As expected, a strong association was found between depression and MCS (B = –13.6 [95% CI –16.6, –10.6]), implying that the presence of a depressive disorder decreased the MCS with >1 SD. A strong association was also found between anxiety and MCS (B = –8.0 [95% CI –14.4, –1.5]). The PCS was not clearly affected by the presence of depression (B = 0.8 [95% CI –1.8, 3.4]) or anxiety (B = –0.1 [95% CI –5.2, 4.9]). After multiple imputation using chained equation, similar results for the association between cognition and HRQoL cross-sectionally were found (see Supplementary Table 7, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24904). Different multiple imputations for missing data on cognitive function also yielded similar results to the main analyses (see Supplementary Table 7). In addition, the association between cognition and HRQoL was assessed longitudinally using linear regression analyses instead of mixed models, which also revealed similar results (see Supplementary Table 8, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.24904).

DISCUSSION

The first aim of our study was to identify the type and severity of cognitive impairment in patients with SLE and NP symptoms of different origins. We demonstrated that objective cognitive impairment is present in approximately one-half of patients who are referred for NP symptoms in SLE and is most pronounced in NPSLE patients with signs of both inflammation and ischemia (combined phenotype). Most patients showed a diffuse pattern of cognitive impairment (multiple domains involved), and this pattern was more frequently seen in patients with NP symptoms of an inflammatory origin. In general, some improvement of cognition was seen over time. The second aim was to identify the association between objective cognitive function and HRQoL. We demonstrated that an association is present, but weak.

Impaired cognitive function in multiple cognitive domains, including executive function and complex attention, has been demonstrated previously in patients with SLE and NPSLE (10,11,33). We have also confirmed this finding in the past in a specific subset of patients of our NPSLE clinic (29). Our current study demonstrated that global cognitive function as measured by the MMSE was impaired in <10% of patients, which is lower than most previous reports, with impairment ranging up to 46% (4). As the MMSE has been developed for severe cognitive dysfunction and dementia, it may be less useful to detect the type of cognitive dysfunction present in patients with SLE. Assessment of the 3 other cognitive domains enabled the detection of more subtle impairment and revealed that cognitive impairment was present in nearly one-half of all patients in each cognitive domain, even though the median SLE duration was only 4 years in our study cohort. Apart from the frequency and severity of cognitive impairment, we also sought to study the pattern of impairment, as this pattern could potentially serve as a tool to distinguish NP symptoms due to inflammation (requiring immunosuppressive treatment) from other origins. We found that the most frequent pattern was a diffuse impairment in multiple domains, and that the patterns were very similar in patients with and without an inflammatory origin, but more frequent in the former. As there are more dimensions to cognition than described in our study, future research should investigate whether there are notable differences in other cognitive domains (e.g., visuospatial processing) between patients with inflammatory and noninflammatory NP symptoms.

Approximately one-third of patients had a follow-up visit at our clinic between 6 months and 2 years. In these patients, a stable or even improved cognition was seen over time. Longitudinal data on cognition in SLE is limited, and changes in all directions have been described (worsening, improvement, no change at all) (34–40). Because in clinical practice we encounter many SLE patients who worry about further cognitive decline, these data provide some reassurance that cognitive decline is limited over 2 years. However, only a subset of patients was seen for follow-up, and therefore the results should be interpreted with caution. The improvement over time that we have identified in our study may be explained in multiple ways: regression to the mean, since in general more severe patients are seen for follow-up, learning effect, as the same neuropsychological tests were performed at

baseline and follow-up, or more interestingly, true improvement over time due to treatment and subsiding of NP symptoms. Further research focusing on the effect of treatment on cognition in patients with SLE is necessary to solve this question.

As cognitive impairment occurs frequently in patients with SLE, we sought to identify its impact on QoL. Several factors related to cognition, such as depression, are known to negatively impact QoL (12,13). HRQoL was low in our study, with average component scores >1 SD lower than those of the general population. This finding is in line with our previous work (41,42). In our current study, we indeed found a strong negative impact of anxiety and depressive disorders on mental components of HRQoL. However, contrary to our expectations and previous research (43), only a weak association appeared to be present between cognition and HRQoL. The few other studies performed to date on this topic have shown a clear association between cognition and HRQoL, but their different designs may explain these seemingly contradictory findings. First, the exposure (cognition) was assessed in different ways in all studies and the outcome (HRQoL) was assessed either with the SF-36 or SF-12 (in 1 study) (16). Second, different methodologic approaches to calculate the effect of cognition on HRQoL were used: correlation coefficients without correction for confounders (14,15) and an analysis of covariance model to predict HRQoL, which also included multiple variables unrelated to cognition (16). Last, 1 study looked at subjective cognitive impairment rather than objective cognitive impairment (14). An individual's perceived limitations in cognition likely associate more strongly with self-assessed HRQoL, and experienced cognitive dysfunction is known to differ strongly from objective cognitive dysfunction in patients with SLE (44). Hence, we hypothesize that HRQoL is influenced by subjective rather than objective cognitive impairment, and patient-reported outcome measures for cognition are perhaps a more useful tool for future intervention trials with QoL as the main outcome.

Our study has several strengths. We present a relatively large, well-defined cohort of patients with SLE and NP symptoms of different origins, and all patients underwent standardized assessment including neuropsychological assessment. Furthermore, we are the first to study the association between cognition and HRQoL in depth in patients with SLE and using different analysis techniques, which confirms the robustness of our findings.

There are also several limitations to acknowledge. First, there were missing data, which could have influenced our study results. Patients with the most severe NP presentations, who were unable to undergo cognitive assessment, were excluded from this study. This exclusion has possibly influenced the comparison between NPSLE phenotypes, as severe NP illness is more often seen as a result of inflammation. Seeing the limited number of patients excluded due to severe illness in general (n = 4, of which 3 had inflammatory NPSLE), we believe that this limitation has not strongly influenced our findings. In addition, sensitivity analyses with different types of imputation for missing data did not alter our study results. Second, only a limited number of patients had a follow-up visit, and follow-up was performed on indication (e.g., initiation of immunosuppressive treatment). Therefore, the improvement of cognition at follow-up should be interpreted with caution, and further research is necessary to identify the pattern of cognition over time. Furthermore, subjective cognition was not measured, which could have resulted in missing more subtle impairment not registered with the cognitive assessment. Last, as patients of this study were from a tertiary referral center for NP symptoms, the frequency of cognitive impairment is not generalizable to the entire SLE population. In addition, although correction was made for important confounders (including anxiety and depression), the associations between cognition and HRQoL may not be generalizable to all patients with SLE.

In conclusion, objective cognitive impairment was found in one-half of patients with SLE and NP symptoms. Patients with an inflammatory origin of NP symptoms generally showed the most severe impairment and more frequently had impairment in multiple domains. Despite cognitive problems being commonly mentioned as a burdensome symptom in clinical practice, only a weak association between HRQoL and objective cognitive function was present.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Monahan had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Analysis and interpretation of data. Monahan, Middelkoop, Groenwold, Kloppenburg, Huizinga, Steup-Beekman.

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